REMARKS

Claim Objections

The Examiner noted gramatical and spelling errors in Claims 42 and 47. Applicants have amended those Claims to correct the problems.

Claim Rejections 35 USC 112

The Examiner has rejected claims 1, 2, 5- 7, 10-14, 16, 19-29 and 30-52 under 35 USC § 112, second paragraph, as being indefinite.

First, with respect to Claims 1, 2, 5 and 10-14, the Examiner contends it is unclear what is meant by characterizing the composition as "non-polymeric." Applicants had intended the amendment to convey the meaning that although the composition could include polymeric portions, the claimed composition as a whole does not consist of repeating units. However, Applicants have removed this term from the claim language to avoid this confusion.

Second, with respect to Claims 6, 7 and 19-29, the Examiner indicated it was unclear what was meant by the term encapsulator. Applicants have amended the claims to clarify that the encapsulator comprises an amphipathic molecule that is subject to pH degradation, and thus it is the amphipathic molecule that comprises a hydrophobic portion and a hydrophilic portion linked by an ortho ester. The Examiner further objected to Claim 16, stating it was unclear what constituted "derivatives" of dichloromethylmethyl ether. Applicants respectfully submit that one having skill in the art would readily recognize that such derivatives must share the basic chemical nature of the named compound, but could have simple substitutions that do not fundamentally alter the characteristics of the compound. For example, such derivatives are clearly limited in a specific manner since they must be capable of forming an ortho ester in the claimed amphipathic composition. An example of such a derivative is shown in Figure 20.

Finally, with respect to Claims 30-52, the Examiner notes that the first occurrence of the term "the hydrophobic portion" lacks antecedent basis. Applicants submit that the amendments to the claims have corrected this problem.

In light of the above amendments and remarks, Applicants request that the Examiner withdraw the rejection of Claims 1, 2, 5- 7, 10-14, 16, 19-29 and 30-52 under 35 USC § 112, second paragraph.

Claim Rejections 35 USC 102

The Examiner has rejected claims 6, 7, 15, 16, 19-21, 24, 25, 30, 31, 34, 38, 39, 42 and 50-52 under 35 USC § 102(e) as anticipated by Nantz et al. The Examiner contends that the Nantz reference teaches lipid formulations having an orthoester that could be used in conditions that would lead to hydrolysis of the orthoester. In the previous response, Applicants added the claim limitation that the ortho ester directly attaches to the hydrophobic portion by an oxygen atom. The Examiner responded by noting that Nantz et al. teaches R_2 of Formula I could be an alkoxy, thereby meeting the added claim limitation. However, under such conditions, the Nantz ortho ester would not satisfy the other claim limitation that hydrolysis of the ortho ester conjugate directly releases the hydrophilic portion.

At the outset, Applicants would like to further emphasize the distinctions between the ortho esters of this invention and those disclosed by Nantz et al. In Applicants' invention, the ortho ester composition is relatively simple. It is an amphipathic molecule comprising a hydrophobic portion joined to a hydrophilic portion by an acid-labile ortho ester linker. In other words, hydrolysis of the ortho ester directly detaches the hydrophilic portion from the hydrophobic portion. Applicants have amended the independent Claims 19, 30, 38, 42, 48 and 50 to clarify that hydrolysis of the ortho ester cleaves it. Applicants have also amended the Claims to remove the limitation that the hydrophobic group attach to an oxygen atom of the ortho ester as the feature is not necessary to distinguish Nantz for the reasons discussed below.

In contrast, Nantz et al. teaches a more complex molecule that undergoes a more complex degradation process. As shown in Figures 1A-E, the Nantz molecule has a hydrophobic domain (B) joined by an ortho ester moiety (A) to a linker (C) which is in turn joined by a cleavable group (D) to hydrophilic head group (E). The chief distinction is that Nantz's molecule is degraded by cleavage of the "cleavable" group (D), not by cleavage of the ortho ester (B). Indeed, this is described in the specification at col. 6, lines 35-62 and illustrated in Figure 2. As one of skill in the art will appreciate, this degradation process is significantly more complex. In Nantz, the ortho ester is not a cleavable linker, rather hydrolysis of the ortho ester first leads to transesterification of molecule which secondarily cleaves group D. This requires careful selection of cleavable group D, which is described in Nantz as the functional group Q, at col. 3, lines 7-10 for example. Thus, Nantz's ortho ester moiety is not cleaved and the Nantz molecules

undergo a completely different and more complex degradation process than that claimed by Applicants.

With respect to the Examiner's observations regarding Nantz's use of an alkoxy group for R_2, Applicants reiterate that the claimed invention uses the ortho ester group as the cleavable linker while Nantz does not teach the use of a cleavable ortho ester, but rather requires a separate cleavable group. This fundamental difference prevents Nantz from meeting all the claimed limitations. Each independent claim at issue, Claims 19, 30, 38, 42, 48 and 50, requires that the ortho ester cleave to release the hydrophilic group from the hydrophobic group *and* the encapsulator. Even if R_2 of Nantz's Formula I is an alkoxy, the possibility advanced by the Examiner, there is still no teaching that the ortho ester cleaves when it is hydrolyzed. Instead, as discussed above, Nantz discloses that hydrolysis of the ortho ester leads to a transesterification reaction that in turn cleaves a distinct functional group, not the ortho ester. Further, even if it were possible for such a molecule to inherently undergo a hydrolysis reaction that would cleave the ortho ester, the hydrophilic group (designated as R_4 in Formula I) would not be released from the encapsulator. Even though R_2 would be released by ortho ester cleavage, R_4 would still be linked to R_1, which is also required to be a hydrophobic group, see col. 2, line 57-60. Thus, R_1 would continue to anchor R_4 to the encapsulator.

Therefore, Applicants respectfully submit that Nantz et al. disclose an ortho ester composition, wherein the ortho ester hydrolyzes but does not cleave. Further, even if the ortho ester were to cleave, the hydrophilic group would not be released from the encapsulator. In contrast, Applicants' claims as amended require both that the ortho ester cleave and that the hydrophilic group be released from the encapsulator as a result of that cleavage. For these reasons, Nantz et al. does not anticipate Claims 6, 7, 15, 16, 19-21, 24, 25, 30, 31, 34, 38, 39, 42 and 50-52 and Applicants respectfully request that the Examiner withdraw this 35 USC § 102(e) rejection.

The Examiner has also maintained the rejection of claims 1, 2 and 10 under 35 USC § 102(b) as being anticipated by Klaveness et al. The Examiner states that Klaveness teaches polymers having the general formula $[(X)_p(R^{10})_q]B$, wherein X is hydrophilic R^{10} is hydrophobic and B is a cross linker that may be an ortho ester. The Examiner concludes that cleavage of the cross linker would inherently separate a hydrophilic group from a hydrophobic group.

Applicants have amended Claim 1 to emphasize a significant distinction between the invention in this application and the teaching of Klaveness et al. Specifically, Claim 1 has been amended to clarify that the claimed composition is amphipathic when joined by the ortho ester linker, but that amphipathic nature is eliminated when the ortho ester is hydrolyzed, separating the composition into two components, one hydrophobic portion and one hydrophilic portion. In contrast, Klaveness teaches a polymer with a base unit $(X)_p(R^{10})_q$ that has an amphipathic nature unaffected by cleavage of the cross linker. Thus, even if a single unit $(X)_p(R^{10})_q$ was cleaved from the polymer by hydrolysis of the cross linker, that single unit still retains its amphipathic nature. Therefore, Applicants respectfully submit that Klaveness et al. do not anticipate Claims 1, 2 and 10 and request that the Examiner withdraw this 35 USC § 102(b) rejection.

Claim Rejections 35 USC 103

The Examiner has rejected claims 1 and 5 under § 103(a) as being obvious over Klaveness in view of Na et al. For the reasons discussed above, Klaveness does not teach or suggest the features of the invention. Since Na teaches only the use of specific types of PEG, it does not compensate for the deficiencies of the Klaveness reference. Thus, Applicants request that the Examiner withdraw the §103 rejection of Claims 1 and 5.

Next, the Examiner has rejected Claims 1, 2, 5, 6, 7, 10, 15, 16, 19-22, 24-32, 34-36, 38, 39, 42 and 50-52 under § 103(a) as being obvious over Zalipsky et al. in view of Nantz et al., Unger et al. and Unger et al. The only teaching of acid-labile ortho esters in this combination of references is from Nantz. Nantz, as discussed above, does not disclose or suggest the invention because it does not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. Since neither the Zalipsky nor either Unger reference is directed to acid-labile ortho esters, they do not supply the teaching missing from Nantz. Therefore, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 1, 2, 5, 6, 7, 10, 15, 16, 19-22, 24-32, 34-36, 38, 39, 42 and 50-52.

The Examiner also rejects Claims 19, 25, 30 and 35 under § 103(a) as being obvious over Nantz et al. in view of Huang et al. Again, Nantz et al. fail as a primary reference because they do not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. The Examiner has cited Huang et al. solely for the teaching of particular lipids that may be used to form liposomes. As such, Huang et al. do not compensate for the noted

deficiencies of Nantz et al. Applicants thus request that the Examiner withdraw this §103 rejection of Claims 19, 25, 30 and 35.

Further, the Examiner has rejected Claims 19, 25, 30 and 35 under § 103(a) as being obvious over Nantz et al. in view of Sankaram et al. As discussed above, Nantz et al. fail as a primary reference because they do not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. Sankaram et al. has been cited for the disclosure of particular liposomes, but they do not suggest degradable ortho esters. As such, the Sankaram et al. reference does not compensate for the noted deficiencies of Nantz et al. Applicants thus request that the Examiner withdraw this §103 rejection of Claims 19, 25, 30 and 35.

The Examiner has also rejected Claims 19, 25, 30 and 35 under § 103(a) as being obvious over Nantz et al. in view of Sprott et al. Nantz et al., for the reasons discussed above, do not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. Sprott et al. teaches only the use of Coenzyme Q, and thus, do not suggest the degradable ortho esters of the invention. As such, Sprott et al. do not compensate for Nantz et al.'s failure to suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 19, 25, 30 and 35.

Next, the Examiner has rejected Claims 1, 2, 5 and 6 under § 103(a) as being obvious over Zalipsky et al. in view of Nantz et al. and Haynes et al. The only teaching of acid-labile ortho esters in this combination of references is from Nantz. Nantz, as discussed above, does not disclose or suggest the invention because it does not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. Since neither the Zalipsky nor the Haynes reference is directed to acid-labile ortho esters, they do not supply the teaching missing from Nantz. Therefore, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 1, 2, 5 and 6.

Similarly, the Examiner has rejected Claims 1, 2, 5 and 6 under § 103(a) as being obvious over Zalipsky et al. in view of Nantz et al. and Sprott et al. The only difference is that the Examiner is citing Sprott for the teaching of coenzyme Q. Nevertheless, Nantz does not disclose or suggest the invention because it does not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. Further, neither the Zalipsky nor the Sprott reference is directed to acid-labile ortho esters so they do not supply the teaching missing from

Nantz. Therefore, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 1, 2, 5 and 6.

Next, the Examiner has rejected Claims 38 and 40 under § 103(a) as being obvious over Nantz et al. in view of Eppstein et al. As discussed above, Nantz et al. do not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. Eppstein et al. is cited for the disclosure of powdered lipid formulations and this does not compensate for Nantz et al.'s failure to suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 38 and 40.

Similarly, the Examiner has also rejected Claims 38, 40 and 41 under § 103(a) as being obvious over Nantz et al. in view of Eppstein et al. and Lishko et al. The Nantz reference does not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. Eppstein et al. is cited for the disclosure of powdered lipid formulations and Lishko for teaching lyophilization. These references do not compensate for Nantz et al.'s failure to suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 38, 40 and 41.

Finally, the Examiner has rejected Claims 42 and 45 under § 103(a) as being obvious over Nantz et al. in view of Needham et al. As discussed above, Nantz et al. do not teach cleavage of an ortho ester linker that results in release of a hydrophilic group from the encapsulator. Needham et al. is cited for the disclosure of dry film compositions and thus does not compensate for Nantz et al.'s failure to suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 42 and 45.

Conclusion

Based on the above remarks and amendments, Applicants submit that the pending claims are patentable and request their early allowance. To expedite prosecution, the Examiner may contact the Applicants representative Nathan Koenig at (541) 806-2252.

Respectfully submitted,

CROSBY, HEAFEY, ROACH & MAY

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